Predictors of Tumor Progression During Neoadjuvant Chemotherapy in Breast Cancer

Abigail S. Caudle, Ana M. Gonzalez-Angulo, Kelly K. Hunt, Ping Liu, Lajos Pusztai, W. Fraser Symmans, Henry M. Kuerer, Elizabeth A. Mittendorf, Gabriel N. Hortobagyi, and Funda Meric-Bernstam

From the Departments of Surgical Oncology, Breast Medical Oncology, Systems Biology, Biostatistics, and Pathology, The University of Texas M.D. Anderson Cancer Center, Houston, TX.

Submitted July 27, 2009; accepted November 30, 2009; published online ahead of print at www.jco.org on March 15, 2010.

Supported in part by Grant No. KG090341 from Susan G. Komen for the Cure (A.M.G.-A.), and Grant No. T32 CA09599 from the National Institutes of Health (A.S.C.).

Presented in part at the 45th Annual Meeting of the American Society of Clinical Oncology, May 29-June 2, 2009, Orlando, FL.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Funda Meric-Bernstam, MD, The University of Texas M. D. Anderson Cancer Center, 1400 Holcombe Blvd, FC 12.3000, Houston, TX 77030; e-mail: fmeric@mdanderson.org.

© 2010 by American Society of Clinical Oncology

0732-183X/10/2811-1821/\$20.00

DOI: 10.1200/JCO.2009.25.3286

ABSTRACT

Purpose

Although most breast cancer patients who receive neoadjuvant chemotherapy (NCT) have a tumor response, a small proportion experience progressive disease (PD). Predictors of response have been reported, but predictors for progression have not been identified. We sought to identify predictors of tumor progression during NCT with the ultimate aim of identifying patients who might benefit from a first-line surgical approach or from novel targeted therapies.

Patients and Methods

Data were obtained from reviewing medical records of patients with stage I to III breast cancer who received NCT (anthracycline and/or taxane based). Statistical analysis was performed to compare patients with any response or stable disease with patients with PD.

Results

One thousand nine hundred twenty-eight patients received NCT; 1,762 patients (91%) had some response, 107 (6%) had stable disease, and 59 (3%) had PD at some point during NCT. Factors predictive of PD included African American race ($P = .002$), tumor (T) status ($P = .002$), and American Joint Committee on Cancer clinical stage ($P = .02$). Histopathologic features of PD were high tumor grade ($P = .005$), high Ki-67 score ($P = .002$), and negative estrogen receptor (ER)/progesterone receptor (PR) status ($P < .001/P < .001$). Pre-NCT T status, race, and ER status were independent predictors of progression in multivariate analysis. Disease progression was a negative predictor of distant disease-free survival and overall survival in multivariate analysis ($P < .001$).

Conclusion

Factors predictive of PD include race, advanced tumor stage, high nuclear grade, high Ki-67 score, and ER/PR negativity. Because many of these variables are also associated with response to NCT, novel molecular predictors are needed to identify patients at risk for progression on standard NCT.

J Clin Oncol 28:1821-1828. © 2010 by American Society of Clinical Oncology

INTRODUCTION

Although neoadjuvant chemotherapy (NCT) has been the standard of care for patients with inflammatory and locally advanced breast cancer, it is increasingly used in patients presenting with operable breast tumors. Results from the National Surgical Adjuvant Breast and Bowel Project B-18 trial and European Organisation for Research and Treatment of Cancer Trial 10902 established the equivalency of NCT and adjuvant chemotherapy with regard to disease-free and overall survival and demonstrated that NCT has the added advantage of increasing breast conservation rates with acceptable local control.¹⁻³ In addition to expanding surgical options and improving cosmetic results, NCT allows oncologists to assess tumor response to therapy and theoretically may also provide early control of micrometastatic disease. Importantly, the ability to

achieve a pathologic complete response (pCR) has been accepted as a surrogate for improved long-term outcome^{1,4-6} and is widely used as the primary end point in NCT trials.

A major concern with the use of NCT is that that even though only a small proportion of patients may have disease progression, tumor upstaging may make breast conservation or even operability impossible. Although many researchers have sought to determine clinical and molecular predictors of a pCR,⁷⁻⁹ none have reported on predictors of progression. Although achieving a pCR confers a survival advantage^{4,6} and tumor downstaging may improve surgical options, discovering pretreatment factors that predict tumor progression may play an even more important role in patient management. The goal of this study was to determine pretreatment variables associated with tumor progression during NCT with the ultimate aim of identifying patients

who might benefit from a first-line surgical approach or from clinical trials with novel targeted therapies rather than standard cytotoxic regimens.

PATIENTS AND METHODS

Patient Population

This study includes patients treated with NCT for adenocarcinoma of the breast at a single comprehensive cancer center between 1994 and 2007. All patients were initially staged based on physical examination, radiologic findings, and pathologic examination of tumor biopsies. Although 3,497 patients were initially identified, we excluded patients who were male ($n = 3$), had inflammatory breast cancer ($n = 357$), had distant metastasis at the time of initial diagnosis ($n = 7$), had axillary metastasis without an identifiable primary breast tumor ($n = 36$), or were being treated concurrently for another primary cancer ($n = 8$). Patients who underwent partial or complete excisional biopsies of their breast primary tumor before initiation of chemotherapy ($n = 226$), who discontinued systemic therapy before tumor response could be assessed ($n = 7$), or whose systemic therapy was managed by another institution ($n = 925$) were also excluded.

This study was approved by the Institutional Review Board of The University of Texas M.D. Anderson Cancer Center, and a prospectively collected database of patients receiving NCT for breast cancer was established. Data were verified by retrospective review of individual patient records, including clinical and radiologic assessments, pathology reports, and operative reports. Determination of clinical response was made based on changes in tumor size seen in radiographic assessment or clinical examination as documented in the medical records. Progression was defined as any increase in tumor size or new development of palpable lymphadenopathy or distant metastasis.

Staging and Treatment

On presentation to our institution, patients underwent physical examination and routine breast imaging, including bilateral mammogram and ultrasound of the affected breast and regional lymph node basins. Magnetic resonance imaging was used selectively. Staging work-up for distant metastasis was performed at the discretion of the treating medical oncologist. For patients whose diagnostic biopsy was performed at an outside institution, pathology slides were obtained and reviewed by our dedicated breast pathologist before initiation of chemotherapy. Immunohistochemistry for Ki-67 was applied to diagnostic needle biopsy samples, and tumor cells were counted (per tumor cell nucleus) by microscopy or image analysis. Chemotherapy consisted of anthracycline- and/or taxane-based regimens as determined by the medical oncology team. Patients were evaluated at regular intervals during their chemotherapy regimens by a multidisciplinary team consisting of medical oncologists, surgical oncologists, radiation oncologists, radiologists, and pathologists to assess clinical response, which guided further treatment decisions.

Statistical Analysis

A logistic regression model was used to estimate probability of progression in a univariate fashion. From this model, an odds ratio (OR) for each prognostic factor was determined with a 95% CI. All potential prognostic factors with $P < .10$ in the univariate analysis were included in a multivariate analysis. Backward elimination method was used to obtain the final model. $P \leq .05$ was considered to be statistically significant. Differences in post-treatment characteristics were analyzed using χ^2 tests and the Fisher-Freeman-Halton test, where appropriate. Median overall survival and distant disease-free survival were determined using the Kaplan-Meier methods. Prognostic factors for survival were then tested for statistical significance using Cox proportional hazards regression model in univariate and multivariate analyses.

RESULTS

A total of 1,928 patients were included; 1,762 patients (91%) had some response (minor, partial, or complete), 107 (6%) had stable disease

(SD), and 59 (3%) had progressive disease (PD) while receiving at least one NCT regimen. For data analysis, patients with any response or SD were grouped together (R/SD) and compared with patients who had PD. Median ages were 49 years (range, 27 to 75 years) for patients with PD and 50 years (range, 25 to 82 years) for patients with R/SD. Seventeen (29%) of 59 patients with PD were African American (AA), whereas 232 (12%) of 1,869 patients with R/SD were AA. There was no difference in menopausal status between the two groups. Demographic data and pretreatment characteristics are listed in Table 1.

Table 1. Patient Demographics and Pretreatment Clinical Characteristics

Demographic or Clinical Characteristic	PD ($n = 59$)		R/SD ($n = 1,869$)	
	No. of Patients	%	No. of Patients	%
Age, years				
Median	49		50	
Range	27-75		22-86	
Menopausal status				
Premenopausal	26	44	823	44
Perimenopausal/postmenopausal	33	56	982	53
Unknown	0	0	64	3
Race				
White	36	61	1288	69
African American	17	29	232	12
Asian	3	5	90	5
Hispanic	2	3	244	13
Other	1	2	15	1
Tumor size, cm				
Median	4.3		3.2	
Range	1.3-10		0.5-20	
T stage				
T1	3	5	286	15
T2	28	47	1,081	58
T3	18	31	250	13
T4	10	17	252	13
N stage				
N0	21	36	728	40
N1	23	39	845	45
N2	5	8	106	6
N3	10	17	190	10
AJCC stage				
I/II/IIA	15	25	758	40
IIB/III/IIIA	26	44	721	39
IIIB/IIIC	18	31	390	21
Histology				
Ductal	50	85	1,596	85
Lobular	4	7	128	7
Mixed	2	3	107	6
Other	3	5	38	2
Nuclear grade				
I/II	16	27	848	45
III	43	73	995	53
Unknown	0		26	1
Ki-67 score*				
Median	60		30	
Range	13-95		0-100	

Abbreviations: PD, progressive disease; R, response; SD, stable disease; AJCC, American Joint Committee on Cancer.

*Ki-67 scores were available in 22 patient in the PD group and 819 patients in the R/SD group.

Pretreatment Characteristics

In the R/SD group, 286 tumors were T1 (15%), 1,081 were T2 (58%), 250 were T3 (13%), and 252 were T4 (13%). Although these numbers were comparable to those in the PD group for T1 ($n = 3$, 5%) and T2 ($n = 28$, 47%) tumors, patients with PD were more likely to have locally advanced T3 ($n = 18$, 31%) or T4 ($n = 10$, 17%) tumors. This correlation with progression was also found when pretreatment tumor size was analyzed as a continuous variable, with the PD group having significantly larger tumors than the R/SD group (median, 4.3 v 3.2 cm, respectively; $P = .001$). Pretreatment nodal status did not predict progression; however, when American Joint Committee on Cancer stage was analyzed, patients in the PD group were more likely to have stage IIIB/IIIC disease than patients in the R/SD group (30.5% v 21%, respectively).

The two groups were also examined for differences between pretreatment histopathologic characteristics. The PD group was more likely to present with high-grade tumors ($n = 43$, 73%) than the R/SD group ($n = 995$, 53%). Patients with PD were more likely to have estrogen receptor (ER) –negative tumors (42 [72%] of 58 patients) and progesterone receptor (PR) –negative tumors (41 [73%] of 56 patients) than patients with R/SD (689 [38%] of 1,820 patients and 889 [49%] of 1,811 patients, respectively). The Ki-67 score was also

higher in patients with PD (median score, 60 for PD v 30 for R/SD). Ductal versus lobular histology did not differ between the two groups. Human epidermal growth factor receptor 2 (HER2) status was also not correlated with progression.

In ongoing NCT trials, regimens are increasingly chosen based on tumor subtype. Therefore, we next evaluated PD rates by tumor subtype (Fig 1A). Of the 224 patients with ER- or PR-positive, HER2-positive tumors, two (0.9%) had PD. Of the 882 patients with ER- or PR-positive, HER2-negative disease, 16 (1.8%) had PD. Of the triple-negative subgroup ($n = 167$; ER-, PR-, and HER2-negative tumors), seven patients (4%) had PD. PD occurred in one (0.7%) of 148 HER2-positive patients receiving trastuzumab-containing regimens

Table 2. Therapeutic Regimens and Post-Treatment Characteristics

Regimen and Surgical Pathologic Characteristic	PD (n = 59)		R/SD (n = 1,869)		P
	No. of Patients	%	No. of Patients	%	
Chemotherapy regimen					
Anthracycline based	57	97	1,711	95	—
Taxane based	57	97	1,423	76	.04
Trastuzumab	2	3	150	8	.21
Surgery*					
BCT	12	20	722	39	< .0001
Mastectomy	40	68	1,119	60	
No surgery	7	12	12	1	
Inoperable	2	3	1	0.05	
Patient refusal	1	2	7	0.4	
Other	4	7	4	0.2	
Tumor size, cm					
Median	4.25		1.6		< .001
Range	0.2-16		0-18		
T stage					
T0	3	5	282	15	< .0001
Tis	0	0	124	7	
T1	10	17	819	44	
T2	22	37	427	23	
T3	12	20	97	5	
T4	4	7	68	4	
Unknown/no surgery	8	14	52	3	
Node stage					
N0	20	34	888	47	.01
N1	24	41	737	39	
N2	5	9	113	6	
N3	3	5	69	4	
Unknown/no surgery	7	12	62	3	
AJCC stage					
0 (pCR)	3	5	338	18	.03
I/II/IIA	21	36	946	51	
IIB/III/IIIA	21	36	401	21	
IIIB/IIIC	6	10	133	7	
Unknown/no surgery	8	14	51	3	
Lymphovascular invasion					
Present†	18	34	411	22	.02
Unknown/no surgery	8	14	40	2	

Abbreviations: PD, progressive disease; R, response; SD, stable disease; BCT, breast-conserving therapy; AJCC, American Joint Committee on Cancer; pCR, pathologic complete response.

*Sixteen patients (1%) in the R/SD group returned to their referring institution for surgical management, so surgery type is unknown.

†Lymphovascular invasion was available in 51 patients (86%) with PD and 1,829 patients (98%) with R/SD.

Fig 1. (A) Tumor response based on estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) subtype. (B) Tumor response in HER2-positive patients receiving chemotherapy regimens with and without trastuzumab. PD, progressive disease; R, response; SD, stable disease.

and in eight (3.3%) of 243 HER2-positive patients receiving NCT without trastuzumab (Fig 1B).

Therapy

Chemotherapy regimens were selected by the medical oncology team. Anthracycline-based regimens were used at similar rates (57 patients [97%] with PD v 1,711 patients [95%] with R/SD). Patients in the PD group were more likely to have received a taxane-based regimen at some point ($n = 57$, 97%) than were patients in the R/SD group ($n = 1,473$, 76%). Forty-five patients had PD while receiving taxanes; progression was noted after one cycle ($n = 9$), two cycles

($n = 21$), three cycles ($n = 4$), or four cycles ($n = 11$). Primary tumor progression was seen in 43 patients, nodal progression was seen in eight patients, and distant metastasis developed in one patient. Twenty-five patients experienced progression while receiving anthracyclines; progression was noted after one cycle ($n = 4$), two cycles ($n = 5$), three cycles ($n = 11$), or four cycles ($n = 5$). Tumor progression was seen in 23 patients, nodal progression was seen in six patients, and distant metastasis developed in one patient.

Because one goal of NCT is to downstage tumors and thus increase the likelihood of successful breast-conserving therapy (BCT), we examined type of surgery. As expected, patients with PD were less

Table 3. Predictors of Tumor Progression

Factor	Univariate Analysis			Multivariate Analysis		
	Odds Ratio	95% CI	P	Odds Ratio	95% CI	P
Age	0.99	0.96 to 1.01	.24			
Menopausal status						
Premenopausal	1.00	—	.82			
Postmenopausal	1.06	0.63 to 1.79				
Race						
White	1.00	—	—	1.00	—	—
African-American	2.62	1.45 to 4.75	.002	2.07	1.12 to 3.84	.02
Hispanic	0.29	0.07 to 1.23	.09	0.29	0.07 to 1.23	.09
Asian	1.19	0.36 to 3.95	.77	1.14	0.34 to 3.84	.84
Other	2.39	0.31 to 18.55	.41	2.65	0.3 to 23.43	.38
Prechemotherapy size	1.17	1.06 to 1.28	.001			
Prechemotherapy T stage						
T1	1.00	—	—	1.00	—	—
T2	2.44	0.74 to 8.07	.14	2.08	0.65 to 6.97	.24
T3	6.77	1.97 to 23.25	.002	6.31	1.81 to 21.97	.004
T4	3.73	1.02 to 13.71	.04	3.07	0.82 to 11.45	.10
Prechemotherapy N stage						
N0	1.00	—	—			
N1	0.94	0.52 to 1.72	.85			
N2	1.65	0.61 to 4.47	.32			
N3	1.83	0.85 to 3.94	.13			
Prechemotherapy stage						
I/II/IIA	1.00	—	—			
IIB/III/IIIA	1.82	0.96 to 3.46	.07			
IIIB/IIIC	2.34	1.16 to 4.68	.02			
ER status						
Negative	1.00	—	—	1.00	—	< .001
Positive	0.23	0.13 to 0.42	< .001	0.24	0.13 to 0.44	
PR status						
Negative	1.00	—	—			
Positive	0.35	0.19 to 0.64	< .001			
HER2 status						
Negative	1.00	—	—			
Positive	0.61	0.29 to 1.27	.18			
Histology						
Ductal	1.00	—	—			
Lobular	0.99	0.36 to 2.81	.99			
Mixed	0.6	0.14 to 2.49	.48			
Prechemotherapy grade						
1/2	1.00	—	—			
3	2.29	1.28 to 4.1	.005			
Ki-67 score	1.03	1.01 to 1.05	< .001			
Taxane-based regimen	2.33	1.05 to 5.16	.04			
Trastuzumab therapy	0.4	0.1 to 1.66	.21			

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

likely to have BCT than were patients with R/SD (20% v 39%, respectively; $P < .0001$). Therapies used in these two groups are listed in Table 2.

Post-Treatment Pathologic Results

The surgical pathologic characteristics of tumors after chemotherapy were compared between the two groups (Table 2). Similar to the pretreatment clinical status, pathologic T stage ($P < .001$) and tumor size were greater in patients with PD than patients with R/SD (median tumor size, 4.25 v 1.7 cm, respectively; $P < .001$). However, even though the pretreatment clinical nodal status did not differ between the groups, the presence of nodal metastasis after NCT was more likely in the PD group (66% for PD v 52% for R/SD; $P = .01$). Similarly, lymphovascular invasion was more prevalent in the PD group (34% for PD v 22% for R/SD; $P = .02$). Final pathologic staging was also worse in the PD group ($P = .03$).

Predictors of Tumor Progression

Univariate analysis of potential predictors of tumor progression is shown in Table 3. Pretreatment characteristics that correlated with progression included AA race ($P < .001$), T stage ($P = .04$), and AJCC clinical stage ($P = .02$). Pretreatment tumor features that correlated with progression were ER negativity ($P < .001$), PR negativity ($P < .001$), high nuclear grade ($P = .005$), and high Ki-67 score ($P < .001$). Treatment with a taxane-based regimen was also associated with tumor progression ($P < .001$). Multivariate analysis was performed using possible predictive variables (identified as those with a $P < .1$) from the univariate analysis. AA race (OR = 2.07; 95% CI, 1.12 to 3.84; $P = .02$), pretreatment clinical T3 status (OR = 6.31; 95% CI, 1.81 to 21.97; $P = .004$), and ER negativity (ER-positive status with OR = 0.24; 95% CI, 0.13 to 0.44; $P < .001$) were the most important predictors of progression in this model (Table 3).

Clinical Outcomes

Distant disease-free survival and overall survival were evaluated with a median follow-up time of 41.75 months (range, 2 to 168 months). Median overall survival time was 3.36 years in the patients with PD and was not reached in the R/SD group (Fig 2). On multivariate analysis, PD was associated with a significantly worse distant

Fig 2. Kaplan-Meier curve of overall survival in patients with progressive disease.

disease-free survival (hazard ratio = 5.06; 95% CI, 3.42 to 7.49; $P < .001$) and overall survival (hazard ratio = 6.22; 95% CI, 4.11 to 9.42; $P < .001$; Table 4).

DISCUSSION

Patients who have a pCR, patients with initially inoperable tumors that become operable, and patients with large tumors that are down-staged to make BCT possible are obvious beneficiaries of NCT, which has led to multiple groups studying predictors of tumor response, mainly focusing on predictors of pCR. The subset of patients who may not be best served by this approach are those who experience disease progression during NCT, given that tumor enlargement may make BCT or even operability impossible and may increase the likelihood of developing metastatic disease. Therefore, delineating predictors of progression during standard chemotherapy is crucial to identify the subset of patients who need an alternative management approach. In this study, we examined clinical and pathologic variables that may predict progression. We found that pretreatment predictors of disease progression include race and features of aggressiveness such as large tumor size, ER and PR negativity, high Ki-67 scores, and high nuclear grade. Not surprisingly, tumors that progressed were more likely to be larger, have nodal metastasis, and have lymphovascular invasion on pathologic evaluation.

Several studies have reported survival differences reported among women of different racial groups with breast cancer. Data from the Surveillance, Epidemiology, and End Results program has shown higher age-adjusted mortality rates for AA women than for white women, with the disparity being particularly pronounced among women younger than age 50 years old.¹⁰ Several social, economic, and biologic factors have been extensively studied to explain the observed racial disparities in survival rates.¹¹⁻¹⁴ Compared with white women, young AA women have a higher incidence of triple-negative tumors, which could, in part, provide a biologic explanation for the poor prognosis among this group of patients.¹² However, we recently examined the pCR rates and early survival outcomes of AA patients with triple receptor-negative breast cancer and found that neither pCR rates nor survival rates were different from those of the non-AA population.¹⁵ This implies that although pCR rates and survival may be similar, there may be a group of AA patients with primary resistant tumors who should be identified and studied to improve their outcome.

Although clinically the PD and R/SD groups were similar before therapy other than tumor size, the patients with PD not only had larger tumors but also were more likely to have nodal metastasis and lymphovascular invasion after NCT, signifying an overall more aggressive biology. Studies from our own institution have shown that extensive residual cancer burden after NCT correlates with poor prognosis.¹⁶ We have also reported decreased 5-year disease-free survival rates when there is residual nodal involvement after neoadjuvant therapy.^{17,18} Predicting tumor progression is necessary to delivery of an effective treatment strategy in these patients with aggressive tumors.

Interestingly, many of the tumor characteristics that correlated with progression in our cohort, such as high grade, ER/PR negativity, and high Ki-67 score, have also been associated with likelihood of complete response to NCT.^{19,20} This suggests that morphologically similar, highly proliferative cancers contain two different

Table 4. Predictors of Survival

Factor	Univariate Analysis			Multivariate Analysis		
	Hazard Ratio	95% CI	<i>P</i>	Hazard Ratio	95% CI	<i>P</i>
Overall survival						
Response status						
R/SD	1.00	—	—	1.00	—	—
PD	6.93	4.67 to 10.27	< .001	6.22	4.11 to 9.42	< .001
Menopausal status						
Premenopausal	1.00	—	—			
Postmenopausal	0.99	0.94 to 1.04	.66			
Prechemotherapy T stage						
T1	1.00	—	—	1.00	—	—
T2	1.47	0.96 to 2.24	.07	1.37	0.90 to 2.10	.15
T3	2.28	1.41 to 3.7	< .001	2.03	1.25 to 3.31	.004
T4	4.50	2.89 to 6.99	< .001	3.28	2.08 to 5.16	< .001
Prechemotherapy N stage						
N0	1.00	—	—	1.00	—	—
N1	2.07	1.54 to 2.77	< .001	1.86	1.38 to 2.52	< .001
N2	3.51	2.32 to 5.29	< .001	2.09	1.35 to 3.24	< .001
N3	4.51	2.96 to 6.89	< .001	3.00	1.93 to 4.67	< .001
ER status						
Negative	1.00	—	—			
Positive	0.50	0.4 to 0.64	< .001			
PR status						
Negative	1.00	—	—			
Positive	0.58	0.45 to 0.74	< .001			
HER2 status						
Negative	1.00	—	—			
Positive	1.05	0.76 to 1.45	.77			
Histology						
Ductal	1.00	—	—	1.00	—	—
Lobular	0.44	0.23 to 0.82	.01	0.49	0.25 to .096	.04
Mixed	1.11	0.68 to 1.82	.67	1.38	0.83 to 2.29	.22
Prechemotherapy grade						
1/2	1.00	—	—	1.00	—	—
3	1.98	1.54 to 2.54	< .001	1.66	1.27 to 2.16	< .001
Ki-67 score	1.016	1.01 to 1.023	< .001			
Taxane-based regimen	1.11	0.86 to 1.43	0.43			
Anthracycline-based regimen	0.88	0.62 to 1.24	0.46			
Lymphovascular invasion	10.42	1.64 to 2.72	< .001	1.016	1.01 to 1.02	< .001
Distant disease-free survival						
Response status						
R/SD	1.00	—	—	1.00	—	—
PD	5.61	3.83 to 8.23	< .001	5.06	3.42 to 7.49	< .001
Menopausal status						
Premenopausal	1.00	—	—			
Postmenopausal	0.89	0.71 to 1.10	.28			
Prechemotherapy T stage						
T1	1.00	—	—	1.00	—	—
T2	1.51	1.03 to 2.22	.04	1.36	0.92 to 2.01	.12
T3	2.30	1.48 to 3.58	< .001	1.86	1.19 to 2.90	.007
T4	3.69	2.43 to 5.60	< .001	2.78	1.81 to 4.26	< .001
Prechemotherapy N stage						
N0	1.00	—	—	1.00	—	—
N1	2.24	1.69 to 2.97	< .001	2.04	1.54 to 2.72	< .001
N2	3.31	2.18 to 5.01	< .001	2.02	1.30 to 3.13	.002
N3	5.49	3.81 to 7.91	< .001	4.06	2.78 to 5.93	< .001
ER status						
Negative	1.00	—	—			
Positive	0.59	0.47 to 0.74	< .001			

(continued on following page)

Table 4. Predictors of Survival (continued)

Factor	Univariate Analysis			Multivariate Analysis		
	Hazard Ratio	95% CI	P	Hazard Ratio	95% CI	P
PR status						
Negative	1.00	—	—			
Positive	0.63	0.50 to 0.79	< .001			
HER2 status						
Negative	1.00	—	—			
Positive	1.11	0.83 to 1.49	.49			
Histology						
Ductal	1.00	—	—			
Lobular	0.76	0.48 to 1.21	.25			
Mixed	1.00	0.62 to 1.61	.99			
Prechemotherapy grade						
1/2	1.00	—	—	1.00	—	—
3	1.53	1.22 to 1.92	< .001	1.28	1.02 to 1.61	.03
Ki-67 score	1.01	1.007 to 1.02	< .001			
Taxane-based regimen	0.91	0.72 to 1.15	.41			
Anthracycline-based regimen	1.27	0.85 to 1.89	.24			
Lymphovascular invasion	2.02	1.59 to 2.55	< .001	1.01	1.00 to 1.02	.002

Abbreviations: R, response; SD, stable disease; PD, progressive disease; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

subpopulations—one that is highly sensitive to chemotherapy (evidenced by the higher pCR rate) and one that is small but highly chemotherapy resistant. Patients with lower grade and ER-positive cancers may not frequently achieve pCR but are also less likely to experience progression during NCT. It is also possible that the decreased rate of progression may be a reflection of the innate slower growth rate seen in this subset of tumors. There remains a need to discover novel molecular markers not only to differentiate highly proliferative tumors that are chemotherapy sensitive from those that are not, but also to identify novel therapeutic targets for these patients with primary resistant disease.

Adjuvant therapeutic decisions are increasingly being guided by available molecular profiling models that use gene expression profiles to predict prognosis.²¹⁻²⁴ Many groups have used gene expression profiles to identify signatures associated with response to specific chemotherapy regimens,^{7,25-28} which in time may translate into clinically applicable models that guide systemic therapy. It is critical to also identify molecular predictors of tumor progression because these patients cannot be identified based on clinicopathologic features alone. The neoadjuvant approach allows for an *in vivo* measure of tumor response and remarkable research opportunities with direct clinical applications to guide the choice of drug administration and the ideal sequence of treatment.

The treatment of breast cancer has been one of the pioneering grounds of individualized cancer therapy. It is standard practice to tailor a patient's treatment based on hormone receptor and HER2 status. This shows an acceptance of the fact that breast cancer represents a heterogeneous group of tumors with highly variable morphologies and responses to therapy. For instance, adding trastuzumab to cytotoxic therapy in HER2-positive patients can improve pCR rates from 26% to as high as 65%.²⁹ These subtypes have different predictors of response, such as high nuclear grade and high Ki-67 score, that are associated with chemotherapeutic response in ER-positive tumors but are not predictive in ER-negative/PR-negative/HER2-negative tumors.^{19,27} Although separating these groups before our statistical analysis would have been ideal, the small proportion of patients with

tumor progression limited the power to determine differences in these subgroups. Even though exposure to a taxane-based regimen was statistically a predictor of tumor progression in our study, this probably reflects a treatment bias. During an early period of patient enrollment, only patients who experienced disease progression on an anthracycline-based regimen were administered a taxane-based treatment in the neoadjuvant setting.

Our study is limited by the fact that it is a retrospective review of a heterogeneous population of patients exposed to a variety of chemotherapy combinations. Patients whose systemic therapy was initiated before presentation at our institution were excluded to allow recording of true pretreatment characteristics. Although it is difficult to assess response in a retrospective fashion, the frequent evaluation of these patients clinically and radiographically allowed assessment of gross response, even though accurate grouping by Response Evaluation Criteria in Solid Tumors (RECIST) criteria was not possible in all patients. Our goal was to determine predictors for progression instead of response, so delineating the degree of response was not necessary. Although outcome is difficult to assess in a population with heterogeneous treatments, disease progression was associated with poor distant disease-free survival and overall survival in multivariate analysis. Prospectively studying patients with uniform chemotherapy protocols would allow exploration of other novel molecular markers.

In our study, patients with PD during NCT were likely to have large, high-grade tumors with negative hormone receptors and high Ki-67 scores. This is exactly the patient population that may benefit the most from chemotherapy based on the possibilities of tumor downstaging and the pathologic markers that have also been associated with complete response. Frequent evaluation of tumor response allows for a switch in chemotherapy combinations to more effective regimens. If there is a possibility that further progression may limit operability or the likelihood of BCT, early termination of systemic therapy to provide surgical control may be the most appropriate course. As more prospective trials are developed to uncover markers for response, it is important to explore correlations with tumor progression and to

identify molecular markers of tumor progression on chemotherapy, which would give significant insight into mechanisms of chemotherapy resistance and might lead to novel targeted agents that would enhance chemotherapy sensitivity in selected patients.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory Role:** Gabriel N. Hortobagyi, Bristol-Myers Squibb (C), Novartis (U) **Stock Ownership:** None **Honoraria:** None **Research Funding:** Gabriel N. Hortobagyi, Novartis **Expert Testimony:** None **Other Remuneration:** None

AUTHOR CONTRIBUTIONS

Conception and design: Ana M. Gonzalez-Angulo, Funda Meric-Bernstam

Administrative support: W. Fraser Symmans, Funda Meric-Bernstam

Provision of study materials or patients: Ana M. Gonzalez-Angulo, Kelly K. Hunt, Lajos Pusztai, W. Fraser Symmans, Henry M. Kuerer, Elizabeth A. Mittendorf, Gabriel N. Hortobagyi, Funda Meric-Bernstam

Collection and assembly of data: Abigail S. Caudle, Ana M. Gonzalez-Angulo, Kelly K. Hunt, Lajos Pusztai, W. Fraser Symmans, Henry M. Kuerer, Gabriel N. Hortobagyi, Funda Meric-Bernstam

Data analysis and interpretation: Abigail S. Caudle, Ana M. Gonzalez-Angulo, Ping Liu, Funda Meric-Bernstam

Manuscript writing: Abigail S. Caudle, Ana M. Gonzalez-Angulo, Kelly K. Hunt, Ping Liu, Lajos Pusztai, Henry M. Kuerer, Elizabeth A. Mittendorf, Gabriel N. Hortobagyi, Funda Meric-Bernstam

Final approval of manuscript: Abigail S. Caudle, Ana M. Gonzalez-Angulo, Kelly K. Hunt, Ping Liu, Lajos Pusztai, W. Fraser Symmans, Henry M. Kuerer, Elizabeth A. Mittendorf, Gabriel N. Hortobagyi, Funda Meric-Bernstam

Final approval of manuscript: Abigail S. Caudle, Ana M. Gonzalez-Angulo, Kelly K. Hunt, Ping Liu, Lajos Pusztai, W. Fraser Symmans, Henry M. Kuerer, Elizabeth A. Mittendorf, Gabriel N. Hortobagyi, Funda Meric-Bernstam

REFERENCES

- Fisher B, Bryant J, Wolmark N, et al: Effect of pre-operative chemotherapy on the outcome of women with operable breast cancer. *J Clin Oncol* 16:2672-2685, 1998
- Bear H, Anderson S, Smith R, et al: Sequential preoperative or postoperative docetaxel added to preoperative doxorubicin plus cyclophosphamide for operable breast cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B-27. *J Clin Oncol* 24:2019-2027, 2006
- van der Hage J, van de Velde C, Julien J, et al: Preoperative chemotherapy in primary operable breast cancer: Results from the European Organization for Research and Treatment of Cancer trial 10902. *J Clin Oncol* 19:4224-4237, 2001
- Guarneri V, Broglio K, Kau S, et al: Prognostic value of pathologic complete response after primary chemotherapy in relation to hormone receptor status and other factors. *J Clin Oncol* 24:1037-1044, 2006
- Jeruss J, Mittendorf E, Tucker S, et al: Combined use of clinical and pathologic staging variables to define outcomes for breast cancer patients treated with neoadjuvant therapy. *J Clin Oncol* 26:246-252, 2008
- Kuerer H, Newman L, Smith T, et al: Clinical course of breast cancer patients with complete pathologic primary tumor and axillary lymph node response to doxorubicin-based neoadjuvant chemotherapy. *J Clin Oncol* 17:460-469, 1999
- Hess K, Anderson K, Symmans W, et al: Pharmacogenomic predictor of sensitivity to preoperative chemotherapy with paclitaxel and fluorouracil, doxorubicin, and cyclophosphamide in breast cancer. *J Clin Oncol* 24:4236-4244, 2006
- Rouzier R, Perou C, Symmans W, et al: Breast cancer molecular subtypes respond differently to preoperative chemotherapy. *Clin Cancer Res* 11:5678-5685, 2005
- Nolen B, Marks J, Ta'san S, et al: Serum biomarker profiles and response to neoadjuvant chemotherapy for locally advanced breast cancer. *Breast Cancer Res* 10:R45, 2008
- National Cancer Institute, Surveillance Research Program, Cancer Statistics Branch: Surveillance Epidemiology and End Results Program (SEER) Stat Database: Mortality-all COD, Public-use with state, total U.S. for expanded races/Hispanics (1990-2001). <http://www.seer.cancer.gov/>
- Ayanian J, Kohler B, Abe T, et al: The relation between health insurance coverage and clinical outcomes among women with breast cancer. *N Engl J Med* 329:326-331, 1993
- Bauer K, Brown M, Cress R, et al: Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: A population-based study from the California Cancer Registry. *Cancer* 109:1721-1728, 2007
- Bradley C, Given C, Roberts C: Race, socioeconomic status, and breast cancer treatment and survival. *J Natl Cancer Inst* 94:490-496, 2002
- Carey L, Perou C, Livasy C, et al: Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. *JAMA* 295:2492-2502, 2006
- Dawood S, Broglio K, Kau S, et al: Triple receptor-negative breast cancer: The effect of race on response to primary systemic treatment and survival outcomes. *J Clin Oncol* 27:220-226, 2009
- Symmans W, Peintinger F, Hatzis C, et al: Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy. *J Clin Oncol* 25:4414-4425, 2007
- Kuerer H, Sahin A, Hunt K, et al: Incidence and impact of documented eradication of breast cancer axillary lymph node metastases before surgery in patients treated with neoadjuvant chemotherapy. *Ann Surg* 230:72-78, 1999
- Pierga J, Mouret E, Dieras V, et al: Prognostic value of persistent node involvement after neoadjuvant chemotherapy in patients with operable breast cancer. *Br J Cancer* 83:1480-1487, 2000
- Faneyte I, Schrama J, Peterse J, et al: Breast cancer response to neoadjuvant chemotherapy: Predictive markers and relation with outcome. *Br J Cancer* 88:406-412, 2003
- Dowsett M, Dunbier A: Emerging biomarkers and new understanding of traditional markers in personalized therapy for breast cancer. *Clin Cancer Res* 14:8019-8026, 2008
- van de Vijver M, He Y, van't Veer L, et al: A gene-expression signature as a predictor of survival in breast cancer. *N Engl J Med* 347:1999-2009, 2002
- Perou C, Sorlie T, Eisen M, et al: Molecular portraits of human breast tumors. *Nature* 406:747-752, 2000
- Paik S, Shak S, Tang G, et al: A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med* 351:2817-2826, 2004
- Acharya C, Hsu D, Anders C, et al: Gene expression signatures, clinicopathological features, and individualized therapy in breast cancer. *JAMA* 299:1574-1587, 2008
- Gianni L, Zambetti M, Clark K, et al: Gene expression profiles in paraffin-embedded core biopsy tissue predict response to chemotherapy in women with locally advanced breast cancer. *J Clin Oncol* 23:7265-7277, 2005
- Thuerigen O, Schneeweiss A, Toedt G, et al: Gene expression signature predicting pathologic complete response with gemcitabine, epirubicin, and docetaxel in primary breast cancer. *J Clin Oncol* 24:1839-1845, 2006
- Chang J, Wooten E, Tsimelzon A, et al: Gene expression profiling for the prediction of therapeutic response to docetaxel in patients with breast cancer. *Lancet* 362:362-369, 2003
- Cronin M, Sangli C, Liu M, et al: Analytical validation of the Oncotype DX genomic diagnostic test for recurrence prognosis and therapeutic response prediction in node-negative, estrogen receptor-positive breast cancer. *Clin Chem* 53:1084-1091, 2007
- Buzdar A, Ibrahim N, Francis D, et al: Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: Results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer. *J Clin Oncol* 23:3676-3684, 2005